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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,625	11/02/2006	Stephen J. Klaus	FP0617 US	7369

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EXAMINER	
OGUNBIYI, OLUWATOSIN A	
ART UNIT	PAPER NUMBER
1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,625	KLAUS ET AL.	
	Examiner	Art Unit	
	OLUWATOSIN OGUNBIYI	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *Claims 1-5, 9-38 and 46-49* is/are pending in the application.

4a) Of the above claim(s) *17,18,37,38,46 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-16,19-33,36,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/17/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment filed 9/8/08 has been entered into the record. Claims 6-8 and 39-45 have been cancelled. Claims 48-49 are new. Claims 1-5, 9-38 and 46-49 are pending. Claims 1-5, 9-16, 19-33, 36 and 48-49 are under examination. Claims 17-18, 37, 38, 46 and 47 are withdrawn.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Information Disclosure Statement

The information disclosure statement filed 9/17/08 has been considered and an initialed copy is enclosed.

Election/Restrictions

Applicants affirm the election made with traverse of Group I claims 1-36 and 39-45 in the telephone restriction of Dec. 7, 2007 and in reply to the restriction requirement in the office action mailed 1/14/08. Applicants traverse on the grounds that due to substantial overlap in subject matter, examination of group 1 and group 2 would not be undue on the examiner. Applicants also affirm election of the species (1) hematopoietic stem cells, (2) hydroxyurea, (3) EGLN, and (4) beta-thalassemia and sickle cell syndrome.

With respect to Applicants traversal, Applicants arguments have been carefully considered but are not persuasive. Applicant is reminded that the instant application is a national stage of an international application i.e. filed under 35 U.S.C 371. As provided in 37 CFR 1.475(a), a

national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. In this case, search burden is not a criteria for restriction.

As stated in the restriction requirement of the previous action, Groups I and II lack unity of invention because the technical feature of Group I is anticipated by the art (Perrine et al, Blood vol. 74 p. 454-459 July 1989) and therefore not "special" within the meaning of PCT Rule 13.2 because it does not provide for a contribution that the claimed invention makes over the art. Perrine et al teaches a method for increasing endogenous gamma globulin in a subject the method comprising administering to the subject sodium butyrate (see abstract, p. 458 columns 1 last bridging paragraph to column 2). In addition, even though the inventions of these groups require the technical feature of an agent that increases expression of the gene encoding gamma globin, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Perrine et al who teaches sodium butyrate that increases endogenous gamma globulin.

The restriction requirement is still deemed proper and is made FINAL.

Claims 17-18, 37, 38, 46 and 47 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/8/08.

Rejections Withdrawn

The rejection of claims 1-16, 19-21, 23-27, 39-43 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1-16, 17-24, 27-3, 34-54, of copending Application No.11/348294 ('294) is withdrawn in view of the amendment to the claims.

The rejection of claims 11 and 39-43 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to claim 11 and the cancellation of claims 39-43.

The rejection of claims 11 and 39-43 under 35 U.S.C. 101 because the claimed recitation of a use (claims 39-43) or recitation of an end result of a method step (claim 11), without setting forth any steps involved in the process is withdrawn in view of the amendment to claim 11 and the cancellation of claims 39-43.

The rejection of claims 1, 10, 11-16, 19-21, 23-25 under 35 U.S.C. 102(b) as being anticipated by Tung et al. WO 97/12855 April 10, 1997 is withdrawn in view of the amendment to the claims.

The rejection of claims 1, 10, 11-16 and 21-26 under 35 U.S.C. 102(b) as being anticipated by Perrine et al WO 93/18671 September 30, 1993 is withdrawn in view of the amendment to the claims.

The rejection of claims 1, 10, 11-16, 21-33 and 36 under 35 U.S.C. 102(b) as being anticipated by Bohmer et al WO 01/12784 A1 22 February 2001 is withdrawn in view of the amendment to the claims.

Claims 1-16, 19, and 21-25 are rejected under 35 U.S.C. 102(a) as being anticipated by Klaus et al. WO 03/053997 A2 published 3 July 2003 as evidenced by Pace et al. Experimental Hematology 2000, 28:283-293 is withdrawn in view of the amendment to the claims

New Rejections Based on Amendment

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-5, 9, 10, 11-16, 19-21, 23-27 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1-9, 10, 11-16, 17-24, 34-56, of copending Application No.11/348294 ('294) . This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim 1 and dependent claims are drawn to a method for increasing endogenous gamma globin (gamma-globin) in a subject, the method comprising administering to the subject hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma -globin.

Claim 1 of the '294 application claims the same invention and is also drawn to method for increasing endogenous gamma globin (y-globin) in a subject in need thereof, the method comprising administering to the subject hypoxia- inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding y-globin.

Claim 10 of the instant application is drawn to a method for increasing the level of fetal hemoglobin , the method comprising administering to the subject HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma-globin. Claim 10 of the '294 application is also drawn to a method for increasing the level of fetal hemoglobin in a subject in

need thereof, the method comprising administering to the subject a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma -globin.

Claim 11 and dependent claims of the instant application is drawn to a method for treating a disorder associated with abnormal hemoglobin in a subject in need thereof, the method comprising administering to the subject a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma globin, thereby increasing the level of fetal hemoglobin in the subject. Claim 11 and dependent claims of the '294 application is also drawn to a method for treating a disorder associated with abnormal hemoglobin in a subject in need thereof, the method comprising administering to the subject a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma globin, thereby increasing the level of fetal hemoglobin in the subject

Claim 34 and dependent claims of the '294 application is the same invention as claim 2 and dependent claims of the instant application . Claim 34 of the '294 application is drawn to A method for increasing endogenous gamma globin (gamma-globin) in a subject in need thereof, the method comprising administering to the subject an a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma-globin, wherein the HIF prolyl hydroxylase inhibitor increases expression of the gene encoding gamma -globin by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha). Claim 2 of the instant application is drawn to a method for increasing endogenous gamma globin (gamma-globin) in a subject, the method comprising administering to the subject hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma –globin wherein the HIF prolyl hydroxylase inhibitor increases expression of the gene encoding gamma -

globin by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha).

Claim 42 of the '294 application is drawn to a method for increasing the level of fetal hemoglobin in a subject in need thereof, the method comprising administering to the subject an a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma-globin, wherein the HIF prolyl hydroxylase inhibitor increases expression of the gene encoding gamma-globin by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha). Claim 10 of the instant application is drawn to a method for increasing the level of fetal hemoglobin , the method comprising administering to the subject HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma-globin. Said HIF prolyl hydroxylase inhibitor inherently increases the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha).

Claim 43 of the '294 application is drawn to a method for treating a disorder associated with hemoglobinopathy in a subject in need thereof, the method comprising administering to the subject an a HIF prolyl hydroxylase inhibitor which increases the level of fetal hemoglobin in the subject, wherein the HIF prolyl hydroxylase inhibitor increases the level of fetal hemoglobin in the subject by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha). Claim 11 of the instant application is drawn to a method for treating a disorder associated with abnormal hemoglobin (a hemoglobinopathy) in a subject in need thereof, the method comprising administering to the subject a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma globin, thereby increasing the level of fetal

hemoglobin in the subject. Said HIF prolyl hydroxylase inhibitor inherently increases the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha).

Claim 48 of the '294 application is drawn to a method for increasing the proportion of fetal hemoglobin relative to non- fetal hemoglobin produced by a cell or population of cells, the method comprising administering to the cell or population of cells an agent which increases expression of the gene encoding gamma-globin, wherein the agent increases expression of the gene encoding gamma-globin by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha). Claim 16 of the instant application is also drawn to a method for increasing the proportion of fetal hemoglobin relative to non- fetal hemoglobin produced by a cell or population of cells, the method comprising administering to the cell or population of cells an agent which increases expression of the gene encoding gamma-globin. Said agent inherently increases expression of the gene encoding gamma-globin by increasing the stability or activity of an alpha subunit of hypoxia inducible factor (HIF alpha).

The claims of the '294 application and the instant claims are drawn to the "same invention" as set forth supra.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for

patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 9-16, 19, 21-25 and 48-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 as evidenced by Pace et al. Experimental Hematology 2000, 28:283-293.

The claims are drawn to a method for increasing endogenous gamma globin (gamma-globin) or increasing fetal hemoglobin levels in a subject, the method comprising administering to the subject hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma -globin.

Klaus teaches a method for increasing endogenous erythropoietin in vitro and in vivo comprising administering a compound that inhibits HIF prolyl hydroxylase enzyme activity (p. 2 paragraph 19) which increase endogenous erythropoietin (see abstract, see p. 3 paragraph 14). Erythropoietin increases expression of the gene encoding gamma globin thus increasing the level of fetal hemoglobin as evidenced by Pace et al. Experimental Hematology 2000, 28:283-293 (see first sentence of abstract and first paragraph of the introduction). Thus, said method of increasing endogenous erythropoietin of Klaus et al will increase endogenous gamma globin and thus increase fetal hemoglobin absent evidence to the contrary. Said agent of Klaus et al which

increases endogenous erythropoietin thus endogenous gamma globin increases the stability or activity of the alpha subunit of hypoxia inducible factor alpha (HIF1, HIF2 and HIF3 and any fragment thereof) by inhibiting hydroxylation of said HIF alpha endogenous to said subject (p.1 paragraph 9). Further, Klaus et al teaches a method for increasing endogenous erythropoietin thus increasing expression of the gamma globin gene by administering an agent which inhibits 2-oxoglutarate dioxygenase enzyme activity such as enzyme activity of EGLN1, EGLN2, EGLN3 or any subunit or fragment thereof or inhibits HIF hydroxylase enzyme activity of HIF hydroxylase enzymes such as EGLN1, EGLN2, EGLN3 (p.2 paragraph 13).

Klaus et teaches said method (which inherently increases fetal hemoglobin as set forth supra) to treat disorders associated with abnormal hemoglobin such as thalassemia major and minor (beta thalassemia), sickle cell disease (sickle cell syndrome, sickle cell anemia) (p. 11 paragraph 80). Said method would result in the increased proportion of fetal hemoglobin producing cells to non-fetal hemoglobin producing cells as erythropoietin acts as the cellular level by increasing gamma gene expression, thus increasing fetal hemoglobin. Said agent of Klaus et al is administered with a second therapeutic agent such as exogenous erythropoietin or G-CSF (p.23 paragraph 187, p. 31 claim 15). The method of Klaus et al is performed in vivo or ex vivo (in vitro) (abstract) and the agent is administered to primates e.g. humans or a cell (p. 1 paragraph 10).

Klaus et al teaches that the compound is an hydroxamate (iron chelator – p. 31 claim 36) or structural mimetics of 2 oxo-glutarate (paragraph 110 p. 14). Said 2 oxoglutarate mimetic will inherently inhibit (HIF) prolyl hydroxylase competitively with respect to 2 oxoglutarate and non-competitively with respect to iron.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 9-16, 19, 20, 21-25 and 48-49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 and

Pace et al. Experimental Hematology 2000, 28:283-293 and Tung et al. WO 97/12855 April 10, 1997.

The claims are drawn to a method for increasing endogenous gamma globin (gamma-globin) or increasing fetal hemoglobin levels in a subject, the method comprising administering to the subject hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma -globin.

Klaus teaches a method for increasing endogenous erythropoietin in vitro and in vivo comprising administering a compound that inhibits HIF prolyl hydroxylase enzyme activity (p. 2 paragraph 19) which increase endogenous erythropoietin (see abstract, see p. 3 paragraph 14). Erythropoietin increases expression of the gene encoding gamma globin thus increasing the level of fetal hemoglobin as evidenced by Pace et al. Experimental Hematology 2000, 28:283-293 (see first sentence of abstract and first paragraph of the introduction). Thus, said method of increasing endogenous erythropoietin of Klaus et al will increase endogenous gamma globin and thus increase fetal hemoglobin absent evidence to the contrary. Said agent of Klaus et al which increases endogenous erythropoietin thus endogenous gamma globin increases the stability or activity of the alpha subunit of hypoxia inducible factor alpha (HIF1, HIF2 and HIF3 and any fragment thereof) by inhibiting hydroxylation of said HIF alpha endogenous to said subject (p.1 paragraph 9). Further, Klaus et al teaches a method for increasing endogenous erythropoietin thus increasing expression of the gamma globin gene by administering an agent which inhibits 2-oxoglutarate dioxygenase enzyme activity such as enzyme activity of EGLN1, EGLN2, EGLN3 or any subunit or fragment thereof or inhibits HIF hydroxylase enzyme activity of HIF hydroxylase enzymes such as EGLN1, EGLN2, EGLN3 (p.2 paragraph 13).

Klaus et teaches said method (which inherently increases fetal hemoglobin as set forth supra) to treat disorders associated with abnormal hemoglobin such as thalassemia major and minor (beta thalassemia), sickle cell disease (sickle cell syndrome, sickle cell anemia) (p. 11 paragraph 80). Said method would result in the increased proportion of fetal hemoglobin producing cells to non-fetal hemoglobin producing cells as erythropoietin acts as the cellular level by increasing gamma gene expression, thus increasing fetal hemoglobin. Said agent of Klaus et al is administered with a second therapeutic agent such as exogenous erythropoietin or G-CSF (p.23 paragraph 187, p. 31 claim 15). The method of Klaus et al is performed in vivo or ex vivo (in vitro) (abstract) and the agent is administered to primates e.g. humans or a cell (p. 1 paragraph 10).

Klaus et al teaches that the compound is an hydroxamate (iron chelator – p. 31 claim 36) or structural mimetics of 2 oxo-glutarate (paragraph 110 p. 14). Said 2 oxoglutarate mimetic will inherently inhibit (HIF) prolyl hydroxylase competitively with respect to 2 oxoglutarate and non-competitively with respect to iron.

Klaus et al does not teach said method for treating a disorder associate with abnormal hemoglobin by administering said HIF prolyl hydroxylase inhibitor and in combination with a hydroxyurea as a second therapeutic agent.

Tung et al teaches a method for increasing endogenous gamma globin and fetal hemoglobin in a patient (in vivo, humans), the method comprising administering to the subject an agent which increases expression of the gene encoding gamma globin (p.1 lines 1-15, p.2 lines 24-33, p. 3, p5 lines 16-24). Tung et al teaches that the agent is administered in

combination with a second therapeutic agent such as hydroxyurea also known to treat abnormal hemoglobin disorders such as beta-hemoglobinopathies (p. 24 lines 4-27).

It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to administer a second therapeutic agent such as hydroxyurea in combination with the HIF prolyl hydroxylase inhibitor used to treat abnormal hemoglobin in the method of Klaus et al because the art teaches (Tung et al) that convention agents such as hydroxyurea can be used in combination with other agents such as those used to increase endogenous gamma globin to treat abnormal hemoglobin disorders.

Claims 1-5, 9-16, 19, 21-33, 36 and 48-49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klaus et al. US 2003/0153503 published Aug 14, 2003, filed Dec. 6, 2002 and Pace et al. Experimental Hematology 2000, 28:283-293 and Bohmer et al WO 01/12784 A1 22 February 2001.

The claims are drawn to a method for increasing endogenous gamma globin (gamma-globin) or increasing fetal hemoglobin levels in a subject, the method comprising administering to the subject hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma -globin.

Klaus teaches a method for increasing endogenous erythropoietin in vitro and in vivo comprising administering a compound that inhibits HIF prolyl hydroxylase enzyme activity (p. 2 paragraph 19) which increase endogenous erythropoietin (see abstract, see p. 3 paragraph 14). Erythropoietin increases expression of the gene encoding gamma globin thus increasing the level of fetal hemoglobin as evidenced by Pace et al. Experimental Hematology 2000, 28:283-293 (see

first sentence of abstract and first paragraph of the introduction). Thus, said method of increasing endogenous erythropoietin of Klaus et al will increase endogenous gamma globin and thus increase fetal hemoglobin absent evidence to the contrary. Said agent of Klaus et al which increases endogenous erythropoietin thus endogenous gamma globin increases the stability or activity of the alpha subunit of hypoxia inducible factor alpha (HIF1, HIF2 and HIF3 and any fragment thereof) by inhibiting hydroxylation of said HIF alpha endogenous to said subject (p.1 paragraph 9). Further, Klaus et al teaches a method for increasing endogenous erythropoietin thus increasing expression of the gamma globin gene by administering an agent which inhibits 2-oxoglutarate dioxygenase enzyme activity such as enzyme activity of EGLN1, EGLN2, EGLN3 or any subunit or fragment thereof or inhibits HIF hydroxylase enzyme activity of HIF hydroxylase enzymes such as EGLN1, EGLN2, EGLN3 (p.2 paragraph 13).

Klaus et teaches said method (which inherently increases fetal hemoglobin as set forth supra) to treat disorders associated with abnormal hemoglobin such as thalassemia major and minor (beta thalassemia), sickle cell disease (sickle cell syndrome, sickle cell anemia) (p. 11 paragraph 80). Said method would result in the increased proportion of fetal hemoglobin producing cells to non-fetal hemoglobin producing cells as erythropoietin acts as the cellular level by increasing gamma gene expression, thus increasing fetal hemoglobin. Said agent of Klaus et al is administered with a second therapeutic agent such as exogenous erythropoietin or G-CSF (p.23 paragraph 187, p. 31 claim 15). The method of Klaus et al is performed in vivo or ex vivo (in vitro) (abstract) and the agent is administered to primates e.g. humans or a cell (p. 1 paragraph 10).

Klaus et al teaches that the compound is an hydroxamate (iron chelator – p. 31 claim 36) or structural mimetics of 2 oxo-glutarate (paragraph 110 p. 14). Said 2 oxoglutarate mimetic will inherently inhibit (HIF) prolyl hydroxylase competitively with respect to 2 oxoglutarate and non-competitively with respect to iron.

While Klaus et al teaches administering the HIF prolyl hydroxylase inhibitor that increases endogenous gamma globulin to cells, Klaus et al does not teach that the cells are derived from bone marrow such as hematopoietic stem cells. Klaus also does not teach administering the HIF prolyl hydroxylase inhibitor to a population of cells thus increasing expression of the gene encoding gamma-globulin and transfusing the gamma globin expressing cells into the subject.

Bohmer et al teaches administration of an agent that increases endogenous gamma globin to cells derived from bone marrow such as hematopoietic stem cells (Claim 1 and 5 p. 17). Bohmer et al teaches am method for increasing the level of fetal hemoglobin in a subject having abnormal hemoglobin such as beta thalassemia and sickle cell syndrome such as sickle cell trait and sickle cell anemia comprising administering to a population of cells (such as hematopoietic stem cells) an agent which increase the number of fetal hemoglobin producing cells (resulting from increased expression of the gene encoding gamma globin) and transferring said cells into the subject (p. 2 lines 10-25, p. 17 claim 1, 5).

As to claims 26 and 27, it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to administer the HIF prolyl hydroxylase inhibitor taught by Klaus et al to increase endogenous gamma globin in cells derived from bone

marrow such as hematopoietic stem cells because Bohmer et al teaches administration of an agent that increases endogenous gamma globin to cells derived from bone marrow such as hematopoietic stem cells and because bone marrow cells such as hematopoietic stem cells.

As to claims 28-33 and 36, further it would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to take said cells derived from bone marrow or said hematopoietic stem cells to which HIF prolyl hydroxylase inhibitor is administered and thus having increased expressing of the gene encoding gamma globulin then transfusing said cells into a subject such as a subject having abnormal hemoglobin such as beta thalassemia and sickle cell syndrome such as sickle cell trait and sickle cell anemia in order to treat said abnormal hemoglobin condition as taught by increasing the level of fetal hemoglobin because Bohmer et al teaches a that that cells treated with an agent that increases fetal hemoglobin (increased expression of gamma globin) can be transfused into a subject to treat abnormal hemoglobin conditions.

Status of Claims

Claims 1-5, 9-16, 19-33, 36 and 48-49 are rejected. No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, either of the examiner's supervisors Shanon Foley (571-272-0898) or Robert Mondesi (571-272-0956) can be contacted.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645